UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

010707

**MEMORANDUM**

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: ID No. 053201. METHYL BROMIDE. Review of Inhalation Acute Neurotoxicity Study in Rat (81-8SS) Submitted to Support Reregistration of Methyl Bromide.

Tox. Chem. No.: 555
PC No.: 053201
Submission No.: S442901
Barcode No.: D192435

FROM: Linnea J. Hansen, Ph.D.
Section IV, Tox. Branch I
Health Effects Division (H7509C)

12/8/93

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THRU: Marion P. Copley, D.V.M., D.A.B.T., Section Head
Section IV, Tox. Branch I
Health Effects Division (H7509C)

12/8/93

CONCLUSIONS:

Methyl bromide vapor administered by inhalation at 0, 30, 100 or 350 ppm for 6 hrs to CD® rats resulted in the following effects:

NOEL: 100 ppm
LEL: 350 ppm, based on decreased activity and alertness as measured by functional observation battery parameters for neurobehavioral effects, decreased motor activity and decreased abody temperature in males and females. A slight decrease in hind-limb grip strength in males may have been treatment-related. All animals were assessed to be normal by 1 week post-exposure.

Classification: Core-Guideline

The study appeared to have been properly conducted and is considered acceptable for regulatory purposes.

ACTION REQUESTED:

The Methyl Bromide Industry Panel submitted for review an acute inhalation neurotoxicity study in rats (MRID 427936-01). This study was required to support reregistration of methyl bromide as outlined in a Data Call-In dated 9-20-91.

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81-8SS/Methyl bromide

Primary Review: Linnea J. Hansen, Ph.D. Linnea J. Hansen 12/3/93
Review Section IV, Tox. Branch I
Secondary Review: Marion P. Copley, D.V.M., D.A.B.T. 12/3/93
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**DATA EVALUATION RECORD**

STUDY TYPE: Acute Neurotoxicity TOX. CHEM. NO.: 555
Species: Rat
Guideline: 81-8 SS

MRID NO.: 427936-01 PC NO.: 053201

TEST MATERIAL: Methyl bromide, technical

SYNONYMS: Bromomethane, Brom-O-Gas®/CAS No. 74-83-9

SPONSOR: Methyl Bromide Industry Panel, Chemical Manufacturers Association, 2501 M Street NW, Washington, DC 20037

STUDY NO.: 92N1197 (Laboratory Project No.)

TESTING FACILITY: Bushy Run Research Center, 6702 Mellon Rd., Export, PA 15632-8902

TITLE OF REPORT: Methyl Bromide: Single Exposure Vapor Inhalation Neurotoxicity Study in Rats

AUTHORS: C.D. Driscoll and J.M. Hurley

REPORT ISSUED: May 27, 1993

CONCLUSIONS:

Doses tested: 0, 30, 100 or 350 ppm as vapor, administered by a single 6-hr inhalation exposure to male and female CD® rats.

NOEL: 100 ppm
LEL: 350 ppm, based on decreased activity and alertness as measured by FOB parameters, decreased motor activity and decreased body temperature in males and females after dosing. A slight decrease in hind-limb grip strength in males may have been treatment-related. Effects were transient and all animals were assessed to be normal by 1-week post-exposure.

Classification: Core-Guideline

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81-8SS/Methyl Bromide

This study appeared to have been properly conducted and is considered acceptable for regulatory purposes.

A signed quality assurance statement was present.

A. MATERIALS

Test Compound: Methyl bromide, technical
Purity: >99% (as det. by sponsor)
Description: colorless gas (odorless except at high concentrations)
Lot No.: RL4 (Great Lakes Chemical Corp.)
Contaminants: not specified

Vehicle: air

Test Animal: Species: rat
Strain: CD®
Source: Charles River Laboratories, Inc., Portage, MI
Age: approx. 7 weeks
Weight: males 189.1 - 239.8 g; females 145.5 - 179.2 g

B. STUDY DESIGN

1. Animal Assignment

Following a 3-week acclimatization period, animals were randomly assigned to the following test groups:

TABLE 1: ANIMAL ASSIGNMENT

| Test Group | Dose Level (ppm) | Number Assigned males | females |
|---|---|---|---|
| Control | 0 | 15 | 15 |
| Low Dose | 30 | 15 | 15 |
| Mid Dose | 100 | 15 | 15 |
| High Dose | 350 | 15 | 15 |

Each dose group was divided into 4 replicates of 3-4 animals per sex which were initiated over 4 consecutive days. Animals were exposed to air or test substance in test chambers for 6 hr and the neurologic examinations performed as described below. 10 animals/sex/group were preserved for gross examination. Neurohistopathology was performed on 6 control and 6 high dose animals as described below.

Prior to and after exposure (except during motor activity or functional observational battery testing), rats

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were housed individually in suspended stainless steel mesh cages. Light cycles were 12 hr on/12 hr off, humidity ranged between 40 - 70% and temperature between 66 - 77°F. Food (Agway® Prolab® Animal Diet 3000) and water were provided ad libitum throughout the study except during exposures.

2. Rationale for Dose Selection

Doses were selected based on previously published studies on effects of acute exposure to methyl bromide. This included studies by (1) Honma et al. (Toxicol. Appl. Pharmacol. 81:183, 1985) in which acute exposure to 188 or 250 ppm caused reduced motor activity immediately after exposure and (2) Torkelson and Rowe in Patty's Industrial Hygiene and Toxicology, Vol. 2, 3rd Ed. p. 3443, 1982) in which an $LC_{50}$ for an 8 hr exposure was estimated at 302 ppm.

3. Generation and Analysis of Test Atmosphere

Exposure Conditions: Stainless steel and glass inhalation chambers (Wahmann Manufacturing Co.) with volumes of 900 L and airflow of 200 l/min (13 air changes/hr) were used. Chamber airflow was monitored with a Dwyer Magnehelic® pressure gauge. Methyl bromide from 10 lb. cylinders was introduced into the chambers through a pressure regulator and flowmeter and diluted with filtered supply air to the appropriate test concentration.

Analysis of Test Atmosphere Concentration: Chamber test material concentrations were analyzed about twice per hr during exposures using flame ionization gas chromatography. Chamber temperature and humidity were also recorded about twice per hour. Particle size (MMAD) measurements were not necessary since methyl bromide is a respirable vapor.

Results - Mean test chamber concentrations for each replicate test group are shown below in Table 2:

TABLE 2: TEST ATMOSPHERE ANALYSIS[1]

| | | PPM IN CHAMBERS | | | |
|---|---|---|---|---|---|
| REPLICATE DAY | 0 | 30 | 100 | 350 |
| 1 MEAN: | <MDL | 33.4±0.6 | 102±0.9 | 344±9.2 |
| 2 MEAN: | <MDL | 33.5±0.6 | 100±0.7 | 342±2.8 |
| 3 MEAN: | <MDL | 33.5±2.1 | 102±1.6 | 342±13.8 |
| 4 MEAN: | <MDL | 32.1±1.7 | 98±2.1 | 347±3.0 |
| 4-DAY MEAN: | <MDL | 33.1±0.68 | 100±1.9 | 344±2.4 |

1 Data from Tables 4 - 7, Appendix 1, study report
MDL = minimum detectable level

Mean test concentrations were within acceptable range of target concentrations. All mean daily measurements taken in high dose chamber were slightly below target (≤2.3% below). The greatest variation was noted at high dose for the Day 3 exposure replicate group (SD = 13). Raw data for the bihourly measurements was not included in the study report.

Nominal methyl bromide concentrations for low, mid and high dose were 46.6, 100 and 320 ppm, respectively.

Temperature measured during each exposure day ranged between 20.8 - 22.0°C and relative humidity ranged between 39.7 - 61.0%. The 4-day temperature means for each dose group were 21.2, 21.2, 21.2 and 20.9°C and for relative humidity were 50.2, 48.2, 54.4 and 445.3% (0, 30, 100 and 350 ppm, respectively).

4. Statistical Analysis

Analyses were performed using BMDP Statistical Software or other computer programs. In all analyses, $p < 0.05$ (two-tailed) was considered to indicate statistical significance.

Levene's test for equality of variances was used to compare quantitative continuous variables among the test groups. Parametric ANOVA was performed when variances were homogeneous. When the F value from ANOVA was significant, t-tests were used. A pooled t-test was used for pairwise comparisons when Levene's test indicated similar variances and parametric ANOVA was significant. Where variances as determined by Levene's test were not homogeneous, a nonparametric ANOVA followed by a separate variance t-test for pairwise comparison was used for analysis.

Nested analysis using repeated measures analysis of variance with dose as grouping factor and test period and intrasession interval as within-subject factors were used to analyze motor activity data. In addition, repeated measures analyses at individual testing intervals with dose as grouping factor and intrasession interval alone as the within-subject factor were performed. A Greenhouse-Geisser correction(epsilon-adjustment factor) was used in the repeated measures analyses. Both the 10- and 30-minute intervals were analyzed statistically. Comparisons of cumulative test session activity for treatment groups were also performed at each testing interval. Cumulative test session activity for each testing interval was analyzed as described above for parametric data.

Fisher's exact test was used to statistically analyze most incidence data and control and high dose histopathology data. In the FOB, data with scores to designate severity were analyzed for group differences using Gamma, Kendall's Tau-B, Stuart's Tau C and Somers' D measures of association.

C. METHODS AND RESULTS:

1. Clinical Observations and Mortality

Animals were observed twice daily for clinical signs of toxicity or mortality.

Results - There was no mortality during this study. Clinical findings related to treatment were noted only among animals at 350 ppm. During exposure high dose animals had increased incidence of drooping eyelids and were more lethargic than controls; however, the incidences of the observations seen during exposure were not included in the study report. Except for the functional observational battery parameters described below which were showed effects for the high dose animals on the day of dosing, no apparent treatment-related clinical effects were observed post-exposure.

2. Body Weights

Body weights were measured weekly during acclimatization, on the day before dosing and post-dosing at 1, 7 and 14 days as part of the functional observational battery.

Results - There were no statistically significant differences in mean body weights of treated animals compared to controls. At the end of the 14-day observation period, mean body weights of males were 315.58, 309.23, 313.79 and 307.67 g and females were 195.24, 195.09, 191.92, 192.83 (at 0, 30, 100 and 350 ppm, respectively).

3. Food Consumption

Food consumption was not recorded in this study.

4. Functional Observational Battery (FOB)

An FOB was conducted within the week prior to dosing, by 3 hrs following dosing (Day 1; peak effect as determined from the results of previous studies) and on Days 2, 8 and 15 of the study. The following parameters were observed:

Autonomic functions including lacrimation, salivation, palpebral closure, ocular prominence, pupillary light reaction, piloerection, respiration, urination and defecation;

Sensorimotor responses to visual, auditory, tactile or painful (pinching) stimuli;

Excitability including reaction to handling and open field behavior, rears, vocalization, level of activity and alertness;

Gait and sensorimotor coordination including open field posture and gait pattern, body position, gait abnormalities, righting reaction, visual placing response and landing foot splay;

Grip strength, fore- and hindlimb;

Clinical observations including convulsions, tremors, unusual behavior, hypo- or hypertonia, emaciation, dehydration, unkempt appearance and deposits around eyes, nose, mouth (see C-1 above).

Body temperature (rectal probe).

Scores for level of arousal, gait abnormality, degrees of palpebral closure, eye prominence, pupil size, lacrimation, salivation, appearance, reaction to various stimuli, visual placing response, body position, breathing pattern and air righting response were based on graded scales which indicated degree of change from controls. Scores were analyzed for statistical significance.

Results - Representative parameters from the FOB session following dosing (Day 1) are shown below in Table 4:

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TABLE 4: FUNCTIONAL OBSERVATIONAL BATTERY (DAY 1)[1]

| | 0 PPM | | 30 PPM | | 100 PPM | | 350 PPM | |
|---|---|---|---|---|---|---|---|---|
| PARAMETER | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| No. animals | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Arousal (inactive/alert) | 2 | 1 | 5 | 1 | 4 | 2 | 12** | 7* |
| Rears | 7.33 | 10.07 | 6.27 | 8.00 | 6.20 | 7.27 | 2.33** | 5.35** |
| Drooping/half-closed eyelids | 1 | 0 | 2 | 0 | 1 | 0 | 14** | 6** |
| Piloerection | 0 | 0 | 0 | 1 | 1 | 1 | 11** | 10** |
| Uncoord. air righting response (back or side) | 3 | 1 | 2 | 1 | 0 | 1 | 6 | 7* |
| Body T, C° | 38.16 | 38.71 | 38.31 | 38.54 | 38.32 | 38.55 | 35.29** | 35.10** |
| Hindlimb grip strength, kg | .61 | .57 | .52* | .54 | .57 | .56 | .47** | .55 |
| Urine pools | 7 | 6 | 4 | 8 | 5 | 8 | 13 | 13 |
| Hunched body position | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 4 |
| Lacrimation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Abnormal respiration | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| No response to tail pinch | 0 | 0 | 0 | 0 | 2 | 0 | 4 | 0 |
| No startle response | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 2 |

1 Data taken from Tables 5 and 9 of study report
* $p \leq 0.05$
** $p < 0.01$

There were no treatment-related effects observed at any FOB parameter at 30 or 100 ppm. However, at 350 ppm, several parameters were significantly affected in both males and females. Parameters that indicated level of alertness and activity were affected. Statistically significant increases in numbers of inactive but alert animals, rears, drooping or partly closed eyelids were observed. Incidence of piloerection was increased and body temperature was reduced in both males and females. Hindlimb grip strength was slightly but statistically decreased in males at low and high dose (15% and 25%, respectively). The study authors did not consider this an effect. TB-I considers the high dose reduction to be a possible, slight treatment-related effect since some parameters such as arousal, rears and drooping/half-closed eyelids appeared to be slightly more affected in males than females. The decreased strength may

have reflected the increased lethargy of those animals.

Animals treated with methyl bromide at all dose levels showed FOB responses comparable to controls when tested at 1 and 2 weeks after exposure.

5. Motor Activity

Motor activity was measured during 300 minute observation periods (120 min. light/180 min. dark) after completion of the FOB on the day prior to dosing (Study Day 0) and postdosing on Study Days 1, 8 and 15. Day 1 measurements were initiated approximately 3 hr after termination of exposure period. Number of movements and total time (seconds) spent in movement during 10- and 30-minute time blocks were recorded. Activity was measured in an automated motor activity unit (San Diego Instruments, Inc.). For each replicate group testing was counterbalanced for dose group to reduce study bias from instrumental or environmental effects. Calibration methods and frequency were not described in this study report.

Results - Mean total movements for each dose group are presented below in Table 5:

TABLE 5: MOTOR ACTIVITY (MEAN CUMULATIVE MOVEMENTS/300 MIN TEST SESSION)[1]

| | 0 PPM | | 30 PPM | | 100 PPM | | 350 PPM | |
|---|---|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Preex. # movm.[2] | 2370.7 | 3285.6 | 2602.9 | 2906.8 | 2736.4 | 3531.2 | 2759.4 | 3015.3 |
| Day 1 # movm. | 1913.2 | 2313.7 | 2900.7 | 2456.9 | 1996.7 | 2464.7 | 404.0** | 553.9** |
| Day 7 # movm. | 2117.1 | 2401.9 | 1910.5 | 2326.8 | 2240.9 | 2656.8 | 1931.7 | 2373.2 |
| Day 14 # movm. | 1929.7 | 2405.7 | 1860.2 | 2234.4 | 2095.7 | 2522.8 | 1891.4 | 2077.2 |

1 Data taken from Tables 12 and 13 of study
2 # movements = mean # test session counts
** $p < 0.01$

Statistically significant, dose-dependent decreases in motor activity compared to controls were observed on Day 1 in males and females at 350 ppm. Motor activity levels of high dose animals measured following exposure were only about 21% and 24% of control activity for males and females, respectively. Decreased activity was observed throughout the session (see Appendix). Motor activity was comparable to controls after 1 week. The decreased motor activity was

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consistent with the FOB parameters indicating reduced activity/alertness levels. No interim measurements were taken during the first week to determine recovery time.

5. Sacrifice/Necropsy/Neurohistopathology

Animal Sacrifice and Processing of Tissues: Ten rats/sex/dose group were anesthetized on Study Day 16 (15 days post-exposure) using Euthanasia-6 Solution (Veterinary Laboratories, Inc.) and perfused in situ with 10% neutral phosphate buffered formalin. Organs of the thoracic and peritoneal cavities were examined grossly for abnormalities. Brains and spinal cords, along with peripheral nerves of the hind limb and heads, were removed and immersed in fixative. Brains were weighed after fixation.

Preserved neural tissues from 6 randomly selected rats/sex in the control and high dose groups were processed for histopathologic examination. Low- and mid-dose specimens were not examined since there were no treatment-related lesions observed at high dose. Sections were taken from brain, spinal cord, Gasserian ganglion, dorsal root ganglion, spinal nerve roots and the sciatic nerve and its branches (tibial, trigeminal, peroneal, sciatic and sural nerves). The following nerve tissues and brain regions were examined histopathologically:

| Brain | | | | Spinal cord | |
|---|---|---|---|---|---|
| X | Meninges | X | Cerebellar w.m. | X | Cervical |
| X | Piriform cortex | X | White matter nos | X | Thoracic |
| X | Frontal cortex | X | Ant. commisure | X | Lumbar |
| X | Parietal cortex | X | External capsule | X | Nerve roots |
| X | Temporal cortex | X | Internal capsule | X | Dorsal rt. gang. |
| X | Occipital cortex | X | Corpus callosum | X | Gasserian gang. |
| X | Septal nuclei | X | Fornix | Peripher. n. | |
| X | Caudate/putamen | X | Cerebellar ctx. | X | Sciatic n. |
| X | Globus pallidus | X | Cerebellar nucl. | X | Tibial n. |
| X | Amygdala | X | Vestibular nucl. | X | Peroneal n. |
| X | Hippocampus | X | Pons | X | Sural n. |
| X | Thalamus | X | Medulla obl. | Other | |
| X | Hypothalamus | X | Olfactory bulb | X | Nasal cavity |
| X | Midbrain | X | Optic n./chiasm | | |
| X | Substantia nigra | | | | |

Fixed tissues were processed by embedding either in glycol methacrylate (sciatic nerve and branches) or in paraffin (all other tissues). Heads were decalcified and nasal cavities paraffin embedded. Sections were stained with hematoxylin/eosin, luxol fast blue or Bielschowsky's technique (methacrylate sections were stained with Bielschowsky's stains, hematoxylin/eosin or toluidine blue).

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Results: There were no treatment-related gross observations noted at necropsy. There was no apparent treatment-related neurohistopathology observed in high dose animals. Vacuolization of some tissues in both sexes (spinal cord, cerebellar white matter, trigeminal tract) was observed at comparable low incidence among controls and high dose specimens.

D. DISCUSSION:

TB-I agreed with the conclusions of the study authors that a NOEL of 100 ppm and LEL of 350 ppm were observed for neurotoxicity following single 6-hr inhalation exposures to methyl bromide. The affected parameters reflected decreased activity (including motor activity) and alertness in both males and females. In addition, body temperature was significantly decreased. Effects on hind-limb grip strength were marginal but statistically significant; TB-I considered this a possible effect of treatment whereas the study authors did not. All the observed effects were completely reversible but the number of days required for recovery could not be determined since testing was not conducted until 1 week after the day of dosing. No neurohistopathologic lesions were observed among the animals examined on Day 16 of the study. Although vacuolization of spinal cord and cerebellum have been reported in other studies in animals treated at higher acute (or prolonged subchronic) doses, the occurrence of these lesions in controls at similar low incidence to high dose animals indicated that in this study, these were not treatment-related effects.

TB-I considered the effects on FOB parameters and motor activity observed in this study to be indicative of neurotoxicity of methyl bromide and not secondary to systemic toxicity. The effects seen in this study occurred without body weight loss or other obvious clinical, gross or microscopic effects other than the activity/arousal levels. The functional deficits seen in this study are similar to those reported in previous studies on methyl bromide. The results of this study allow determination of neurotoxicity NOEL and LEL for acute exposure to methyl bromide.

This study appeared to have been properly conducted and is considered acceptable for regulatory purposes.

Classification: Core-guideline



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# APPENDIX 1

TABLE 15
METHYL BROMIDE: SINGLE EXPOSURE VAPOR INHALATION NEUROTOXICITY STUDY
IN RATS

SUMMARY OF MOTOR ACTIVITY DATA
30 MINUTE INTERVAL COUNTS - SUM OF ALL COUNTERS
3 HOURS POSTEXPOSURE

MALES

| GROUP: (PPM) | 0 | 30 | 100 | 350 |
|---|---|---|---|---|
| 0 TO 30 MINUTES | | | | |
| MEAN | 635.5 | 354.9 | 349.8 | 21 |
| S.D. | 164.1 | 181.30 | 191.68 | 32.69 |
| N | 15 | 15 | 15 | 15 |
| 30 TO 60 MINUTES | | | | |
| MEAN | 9.6 | 84.6 | 67.7 | 6.1 |
| S.D. | 17.89 | 185.31 | 109.86 | 11.32 |
| N | 15 | 15 | 15 | 15 |
| 60 TO 90 MINUTES | | | | |
| MEAN | 74.2 | 39.0 | 88.6 | 6.1 |
| S.D. | 119.00 | 34.53 | 123.50 | 10.64 |
| N | 15 | 15 | 15 | 15 |
| 90 TO 120 MINUTES | | | | |
| MEAN | 111.9 | 92.1 | 162.7 | 27.6 |
| S.D. | 154.01 | 79.73 | 246.07 | 57.33 |
| N | 15 | 15 | 15 | 15 |
| 120 TO 150 MINUTES | | | | |
| MEAN | 272.7 | 330.7 | 307.7 | 46.8 |
| S.D. | 147.09 | 205.41 | 124.86 | 52.29 |
| N | 15 | 15 | 15 | 15 |
| 150 TO 180 MINUTES | | | | |
| MEAN | 178.9 | 245.1 | 226.8 | 27.8 |
| S.D. | 163.33 | 166.02 | 199.44 | 36.36 |
| N | 15 | 15 | 15 | 15 |
| 180 TO 210 MINUTES | | | | |
| MEAN | 232.9 | 211.0 | 226.3 | 49.1 |
| S.D. | 186.87 | 104.03 | 191.76 | 97.78 |
| N | 15 | 15 | 15 | 15 |
| 210 TO 240 MINUTES | | | | |
| MEAN | 211.4 | 203.8 | 168.2 | 86.3 |
| S.D. | 147.24 | 163.02 | 133.75 | 153.15 |
| N | 15 | 15 | 15 | 15 |
| 240 TO 270 MINUTES | | | | |
| MEAN | 250.7 | 278.6 | 172.3 | 56.1 |
| S.D. | 265.17 | 161.63 | 143.85 | 75.15 |
| N | 15 | 15 | 15 | 15 |
| 270 TO 300 MINUTES | | | | |
| MEAN | 135.5 | 150.9 | 226.6 | 80.1 |
| S.D. | 111.15 | 100.12 | 140.52 | 83.46 |
| N | 15 | 15 | 15 | 15 |

A statistically significant dose effect on the time versus activity profile of the data was indicated by repeated measures analysis

Data from Table 15 of study report

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Appendix I (cont)

TABLE 19
METHYL BROMIDE: SINGLE EXPOSURE VAPOR INHALATION NEUROTOXICITY STUDY
IN RATS

SUMMARY OF MOTOR ACTIVITY DATA
30 MINUTE INTERVAL COUNTS - SUM OF ALL COUNTERS
3 HOURS POSTEXPOSURE

FEMALES

| GROUP: (PPM) | 0 | 30 | 100 | 350 |
|---|---|---|---|---|
| 0 TO 30 MINUTES | | | | |
| MEAN | 489.3 | 456.5 | 510.4 | 49.6 |
| S.D. | 167.09 | 188.83 | 116.15 | 44.99 |
| N | 15 | 15 | 15 | 15 |
| 30 TO 60 MINUTES | | | | |
| MEAN | 119.1 | 71.3 | 141.5 | 17.3 |
| S.D. | 233.27 | 101.05 | 166.08 | 53.30 |
| N | 15 | 15 | 15 | 15 |
| 60 TO 90 MINUTES | | | | |
| MEAN | 179.3 | 170.0 | 121.0 | 13.3 |
| S.D. | 201.89 | 117.65 | 115.71 | 22.66 |
| N | 15 | 15 | 15 | 15 |
| 90 TO 120 MINUTES | | | | |
| MEAN | 179.5 | 164.3 | 190.2 | 29.8 |
| S.D. | 206.96 | 207.99 | 232.10 | 56.09 |
| N | 15 | 15 | 15 | 15 |
| 120 TO 150 MINUTES | | | | |
| MEAN | 317.1 | 294.4 | 347.4 | 86.7 |
| S.D. | 230.46 | 171.64 | 188.90 | 110.96 |
| N | 15 | 15 | 15 | 15 |
| 150 TO 180 MINUTES | | | | |
| MEAN | 227.1 | 237.7 | 235.5 | 78.9 |
| S.D. | 107.46 | 248.74 | 137.52 | 90.84 |
| N | 15 | 15 | 15 | 15 |
| 180 TO 210 MINUTES | | | | |
| MEAN | 193.5 | 303.1 | 319.2 | 41.1 |
| S.D. | 124.94 | 244.19 | 212.24 | 50.12 |
| N | 15 | 15 | 15 | 15 |
| 210 TO 240 MINUTES | | | | |
| MEAN | 256.7 | 199.7 | 164.2 | 104.7 |
| S.D. | 144.66 | 119.64 | 96.24 | 83.38 |
| N | 15 | 15 | 15 | 15 |
| 240 TO 270 MINUTES | | | | |
| MEAN | 147.6 | 270.1 | 271.1 | 54.9 |
| S.D. | 149.43 | 260.23 | 179.74 | 80.38 |
| N | 15 | 15 | 15 | 15 |
| 270 TO 300 MINUTES | | | | |
| MEAN | 205.4 | 289.7 | 164.2 | 77.6 |
| S.D. | 175.93 | 206.87 | 121.90 | 106.96 |
| N | 15 | 15 | 15 | 15 |

A statistically significant dose effect on the time versus activity profile of the data was indicated by repeated measures analysis

Data taken from Table 19 of study report

# END